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Safety and Feasibility of Rhenium-186 NanoLiposome (^{186}RNL) in Recurrent Glioma: the ReSPECT™ Phase 1/2a Trial

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Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Any statement in this document that is not a historical fact is a “forward-looking statements” within the meaning of Section 27A of the Securities Act & Section 21E of the Securities Exchange Act & are usually identified by the use of words such as “anticipates,” “believes,” “estimates,” “expects,” “intends,” “may,” “plans,” “projects,” “seeks,” “should,” “will,” & variations of such words or similar expressions. We intend these forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act & Section 21E of the Securities Exchange Act of 1934, as amended, & are making this statement for purposes of complying with those safe harbor provisions. These forward- looking statements reflect our current views about our plans, intentions, expectations, strategies & prospects, which are based on the information currently available to us & on assumptions we have made. Although we believe that our plans, intentions, expectations, strategies & prospects as reflected in or suggested by those forward-looking statements are reasonable, we can give no assurance that the plans, intentions, expectations or strategies will be attained or achieved. Furthermore, actual results may differ materially from those described in the forward-looking statements & will be affected by a variety of risks & factors that are beyond our control.

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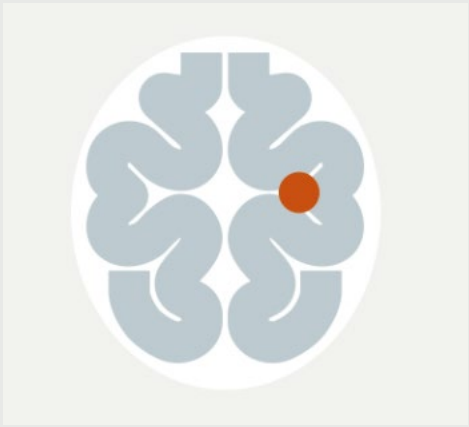
Rare and Difficult-to-Treat Cancers

Responsible for Substantial Morbidity and Mortality Worldwide

+ Rare cancers represent 27% of all cancers; all pediatric cancers are rare
+ Rare cancers account for 25% of all cancer deaths; 5-year survival rate is lower for patients with a rare cancer than those with a more common cancer
+ Treatments for rare cancers are eligible for orphan drug designations

Central Nervous System Tumors



Glioblastoma: Deadliest, most common brain cancer in adults

Leptomeningeal Metastases: Late complication in 5% of cancer patients

Pediatric Brain Cancer: 2nd most common type of cancer in children

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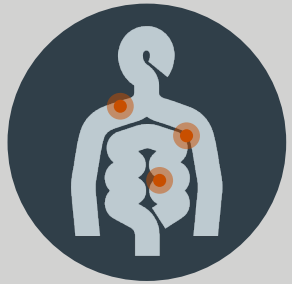
Sources: CBTRUS Statistical Report, NBTS, NCI

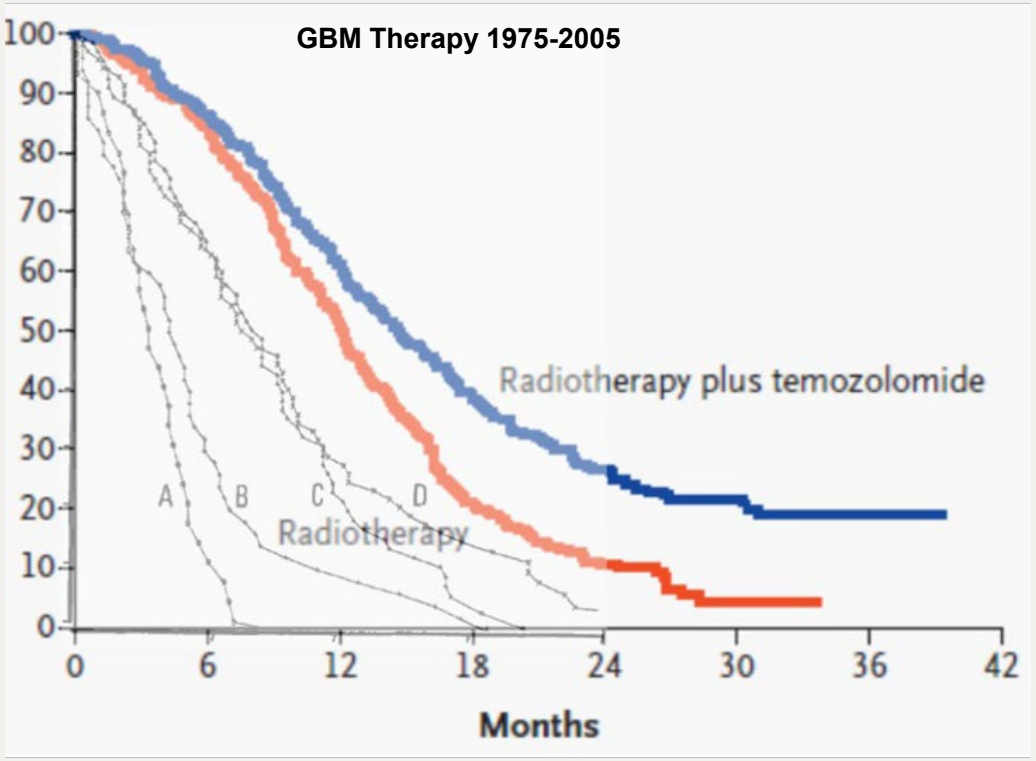
Radiation for GBM

Types of Radiation

External Beam Radiation



Internal Targeted Radiation



- Up to a point, survival time for external beam radiation correlates with the total dose delivered.
- The therapeutic window for external beam radiation is limited by increasing late normal tissue damage.
- Due to the short path length and dose rates, intra-tumoral beta emitters have the potential to dramatically widen the therapeutic window, increase delivered dose, and extend survival time.

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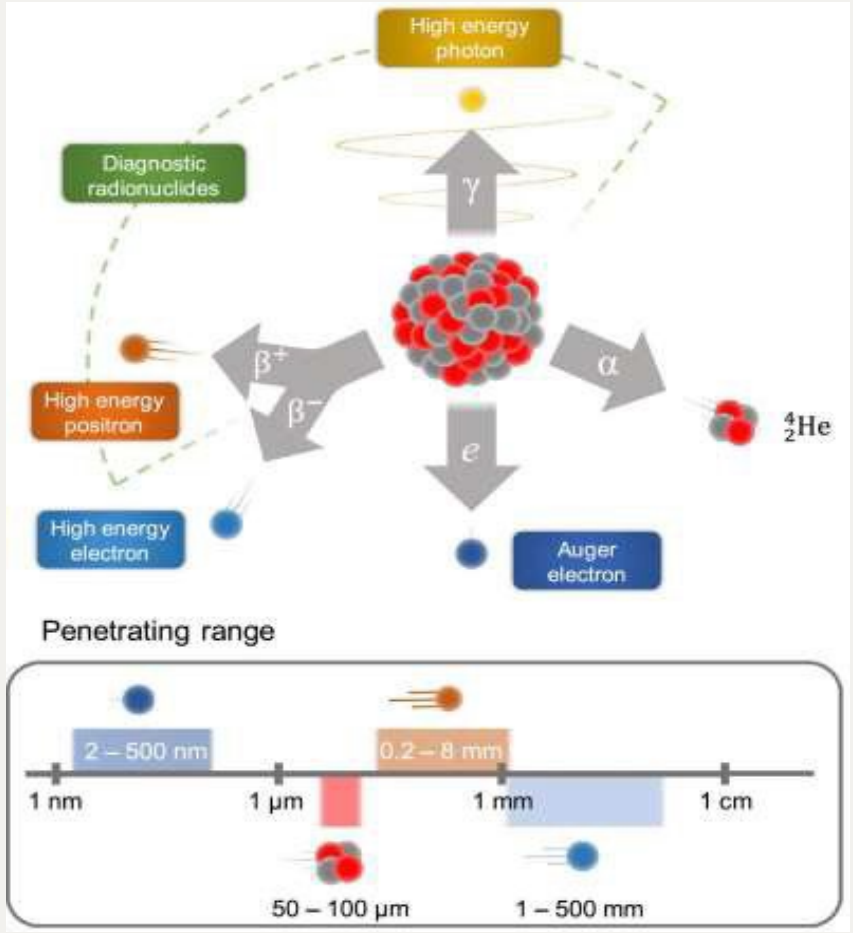
Direct Radiation Therapy with Rhenium-186



- Rhenium-186 (Re-186, 186Re)
- 89.3-hour half-life (3.72 days)
- Beta energy: 1077 keV (71%), 939 keV (22%)
- Gamma energy: 137 keV (9%)
- Max. penetration in tissue: 4.5 mm (average 1.1 mm)16

Absorbed Radiation and Recurrent GBM	
MODALITY	**DS DNA BREAKS**
EBRT (35 Gy)	700-1,400
^{186}RNL (600 Gy)	**12,000-24,000**

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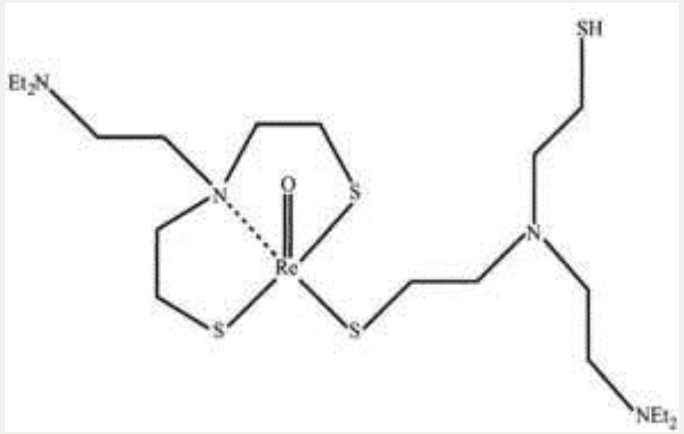
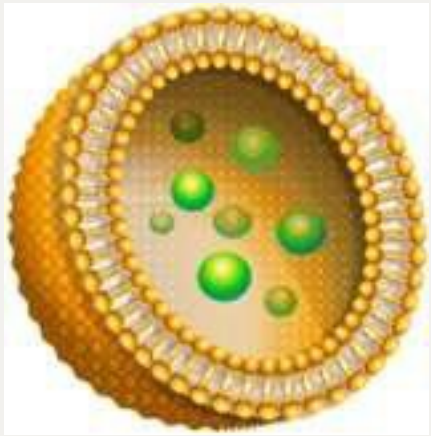
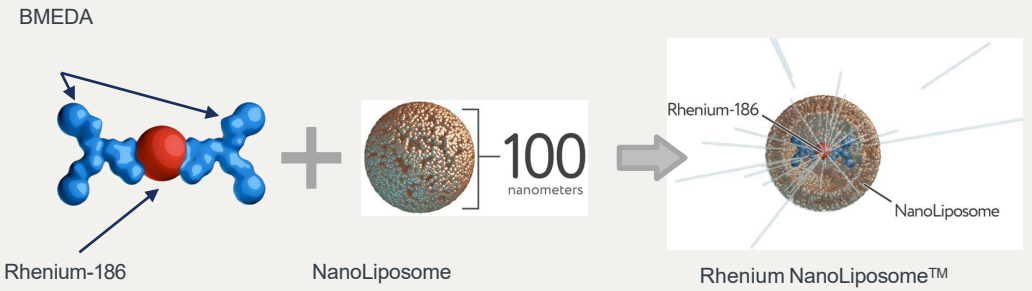
^{186}RNL: A NanoLiposomal Radiotherapeutic

N,N-bis(2-mercaptoethyl)-N',N'-diethyl-ethylenediamine (BMEDA)-chelated ^{186}Rhenium encapsulated within lipid vesicles (nanoliposomes)







- BMEDA is an SNS pattern ligand with a tridentate structure that has one nitrogen and three sulfur atoms. These three atoms donate electrons to 186Rhenium, resulting in a lipophilic complex in a neutral state.
- Nanoliposomes are composed of an 80-130 nm diameter lipid bilayer o distearoylphosphatidylcholine (DSPC) and cholesterol and confer drug delivery control on the chelated ^{186}Rhenium
- ^{186}Rhenium is an ideal radioisotope for therapy with imaging capabilities (SPECT), safety similar to 131I, and penetration in tissue averaging 1.1 mm
- ^{186}RNL manufactured under GMP

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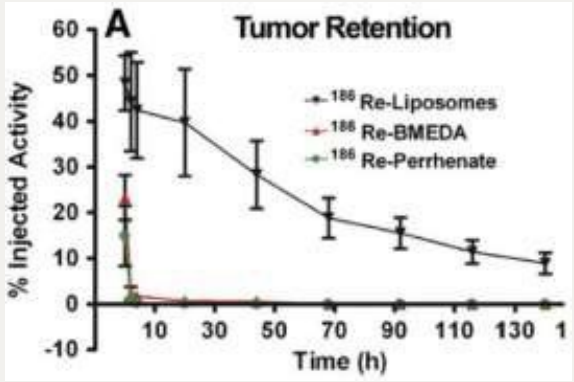
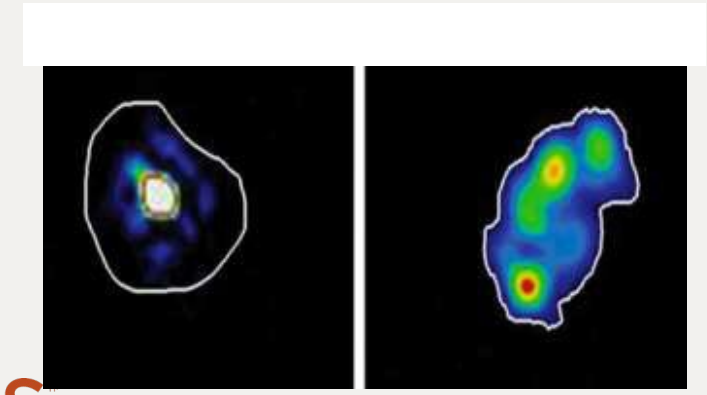
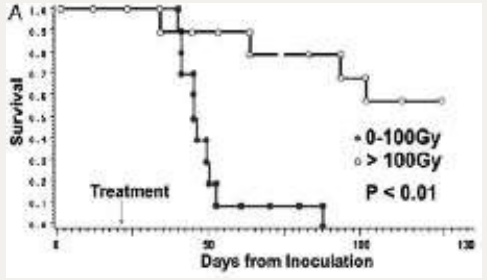
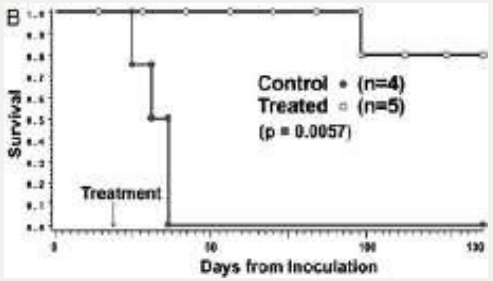
^{186}RNL Preclinical: Retention, Tumor Coverage, Efficacy, Safety

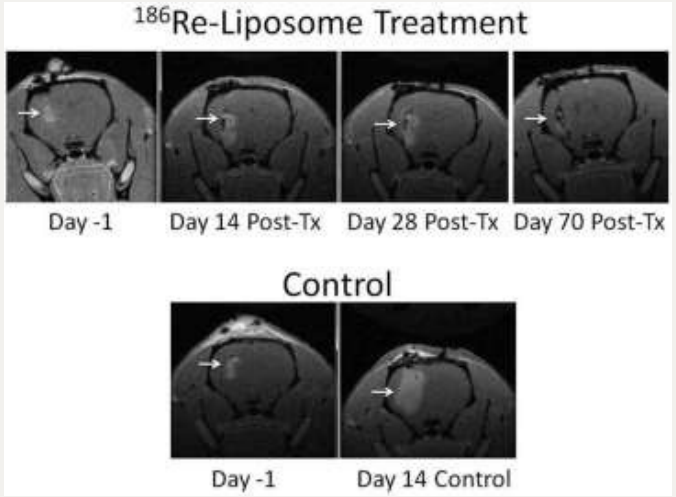
Liposomal encapsulation fundamentally changes both the **retention** within the tumor and the **dispersion** of the drug product.











- Intracranial administration of 1, 3.5, or 6 mCi ^{186}RNL produced **no significant pathologic changes** at 24 hours or 14 days
- Highest absorbed dose was **360 Gy**
- Based on these data, the no adverse effect limit (**NOAEL**), as related to brain pathology, was determined to be an **absorbed dose of 360 Gy**

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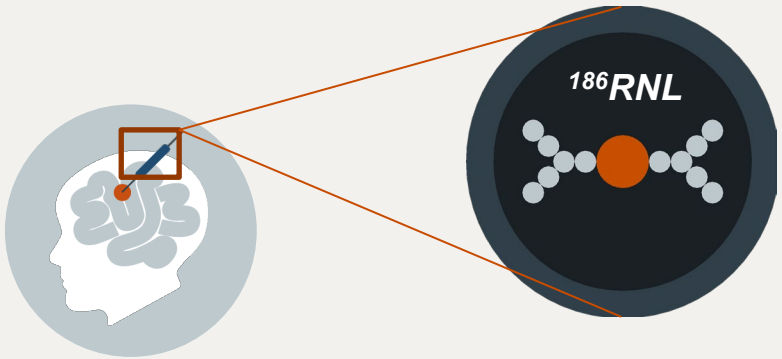
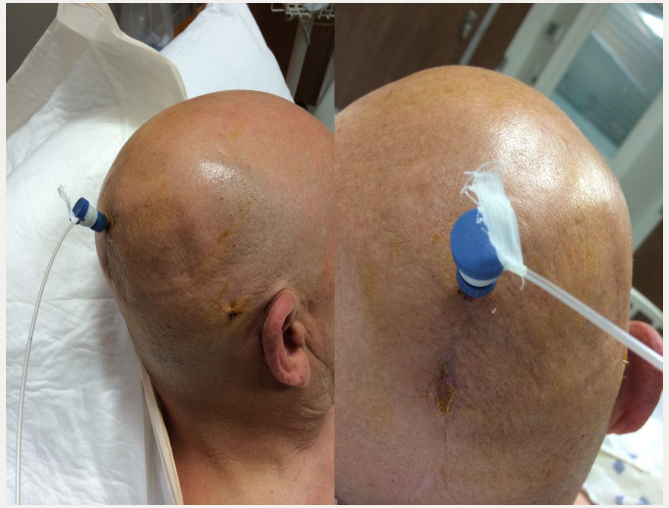
ReSPECT-GBM Phase 1/2a Trial

Direct ^{186}RNL Infusion By Convection Enhanced Delivery

- Multi-center, sequential cohort, open-label, volume and dose finding study of the safety, tolerability, and distribution of ^{186}RNL given by convection-enhanced delivery to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment
- Phase 1 Dose Escalation Study
- Phase 2 Efficacy Study
- Supported by a National Institutes of Health (NIH)
- 5 Sites



Convection-Enhanced Delivery of ^{186}RNL Direct to the Brain Tumor



Convection Enhanced Delivery: *A technique that generates a pressure gradient to deliver therapeutics through the interstitial spaces of the CNS*

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NIH National Institutes of Health

UT Health San Antonio

UT Southwestern Medical Center

The University of Texas MD Anderson Cancer Center Making Cancer History

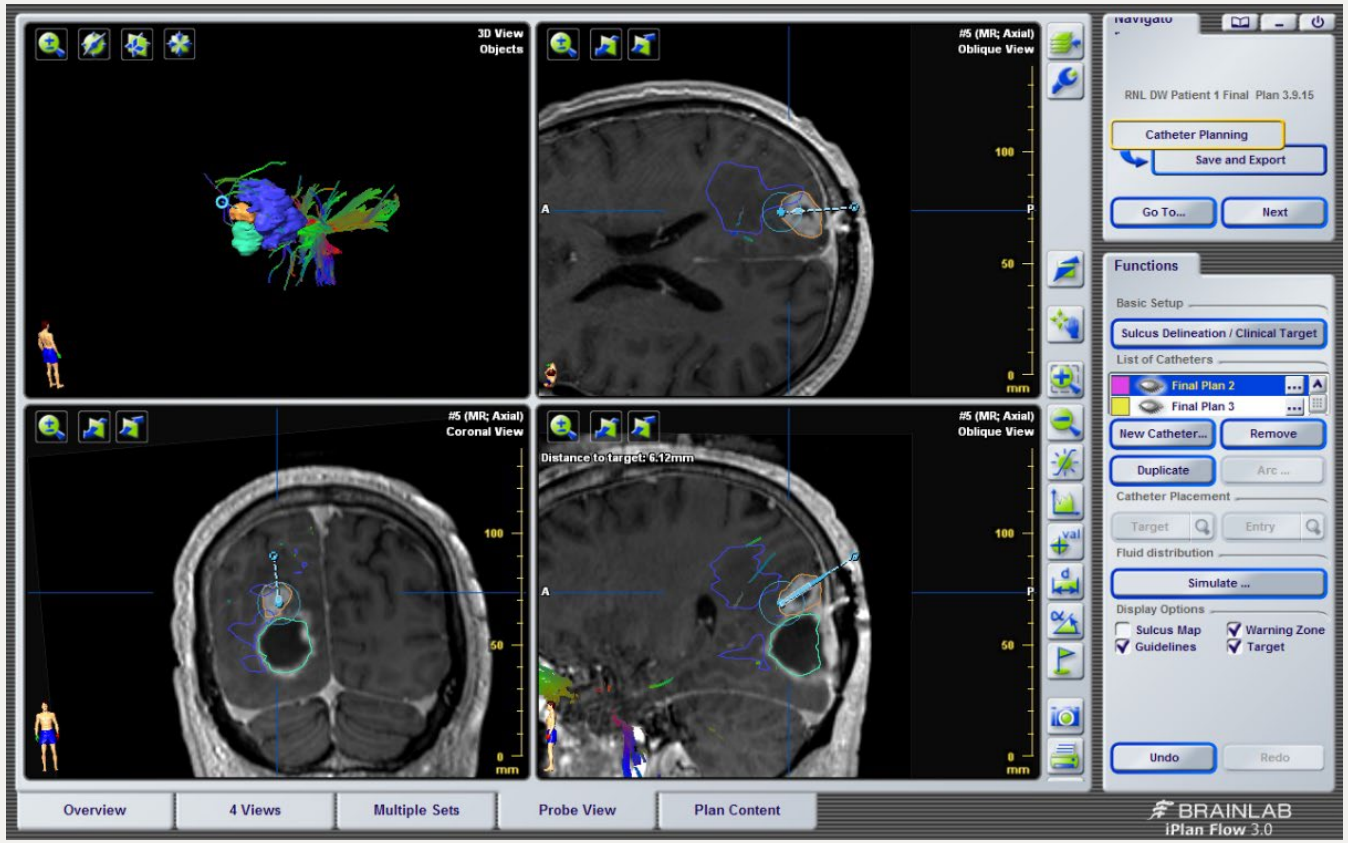
ReSPECT-GBM Phase 1/2a Trial

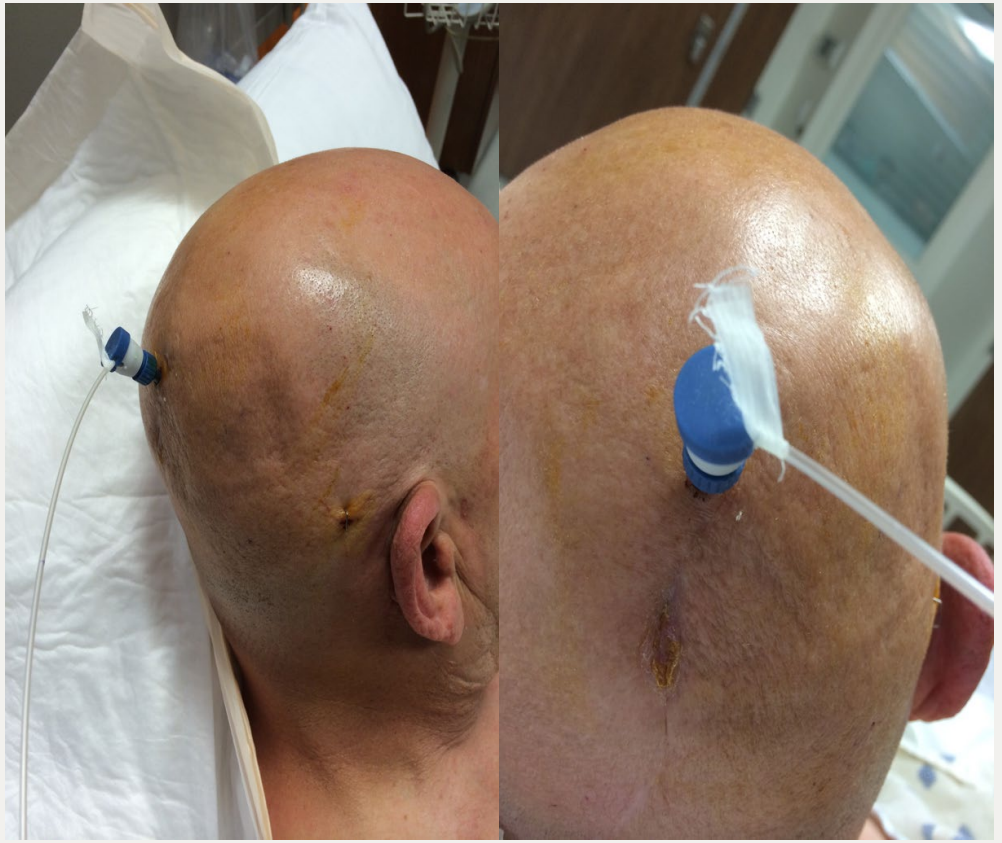
Inclusion / Exclusion Criteria

- No prior bevacizumab (excluded from Cohort 5 onward)
- Progression by RANO criteria following both standard combined modality treatment with radiation and temozolomide chemotherapy
- Patients who receive treatment with antiepileptic medications must have a 2-week history of stable dose of antiepileptic without seizures prior to dosing
- Patients with corticosteroid requirements to control cerebral edema must be maintained at a stable or decreasing dose for a minimum of two weeks without progression of clinical symptoms
- A volume of enhancing tumor which falls within the treatment field volume being evaluated in the respective cohort
- Restricted to glioblastoma from Cohort 6 forward (1 patient with AO and 1 with AA in early cohorts)
- Standard organ function requirements
- ECOG 0-2

ReSPECT-GBM Phase 1/2a Trial

Treatment Planning – MRI-Guided Catheter Placement for ^{186}RNL Infusion by CED





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ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation

Cohort	Infused Volume (mL)	Total ^{186}RNL Activity	Concentration (mCi/mL)	Average Absorbed Dose (Gy)	Status
1	0.66	1.0	1.5	198	Enrolling Cohort 8 (n=24 subjects)
2	1.32	2.0	1.5	122	
3	2.64	4.0	1.5	243	
4	5.28	8.0	1.5	171	
5	5.28	13.4	2.5	423	
6a	8.80	22.3	2.5	287	
6b*	8.80	22.3	2.5	584	
7	12.3	31.2	2.5	In analysis	
8	16.34	41.5	2.5	TBD	

*Cohort 6b utilized the same volume and dose as Cohort 6a but with an increase in maximum flow rate to 20 microliters/minute.

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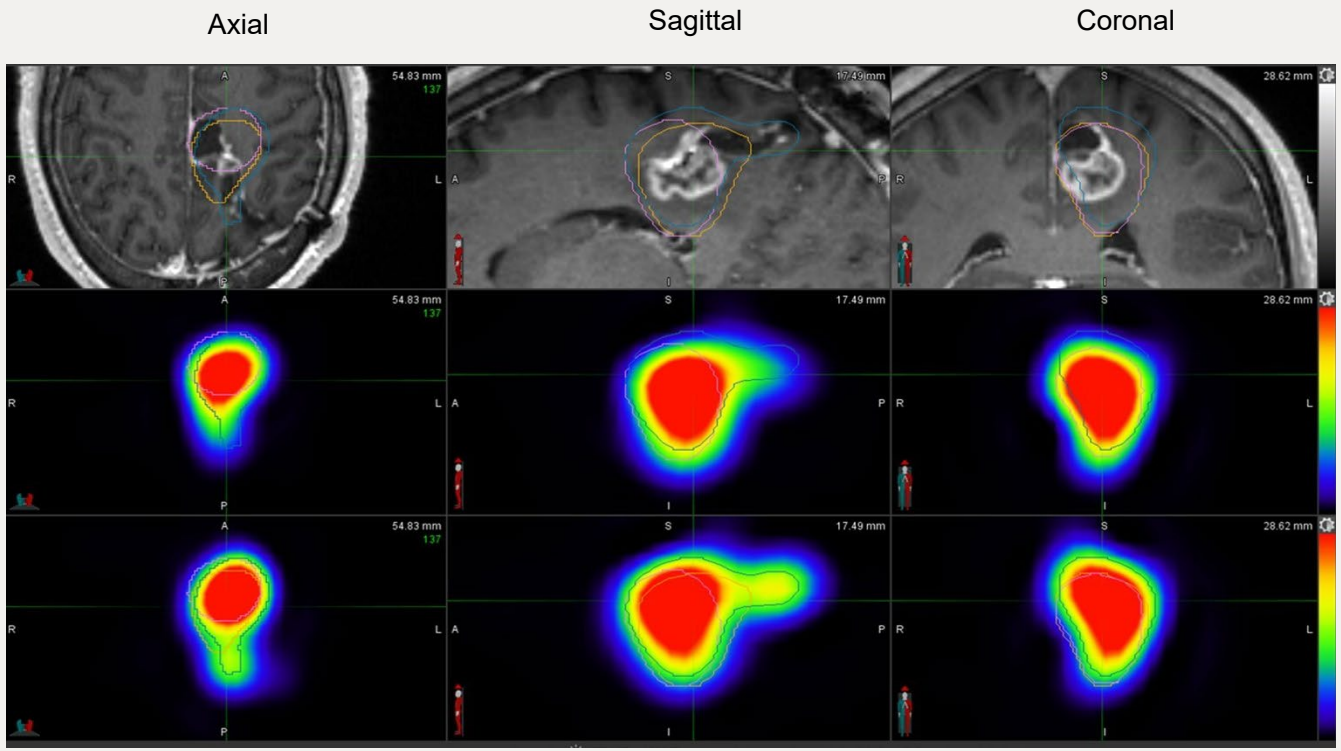
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Subject 01-014



+ Tumor volume was 6.5 mL and tumor coverage was >90%
+ Absorbed dose delivered to tumor was 419 Gy

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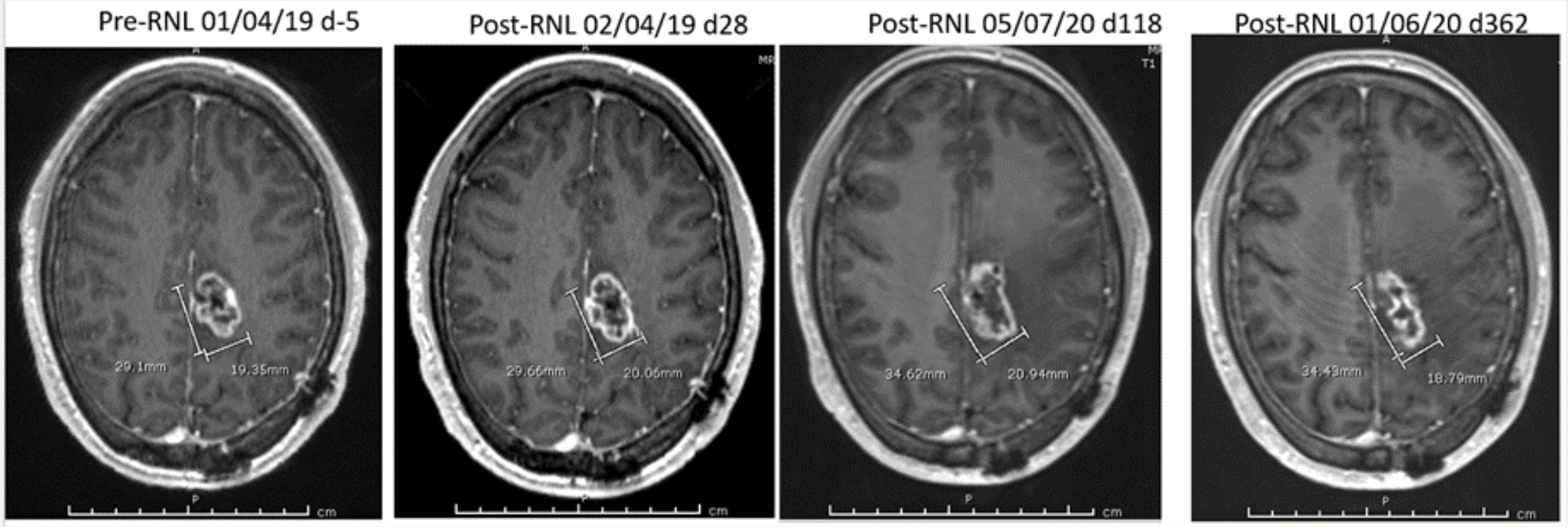
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Subject 01-014



- MRI scans revealed an initial increase in size which peaked at Day 118, with some associated edema, followed by tumor shrinkage out to at least Day 362
- Patient survival >950 days

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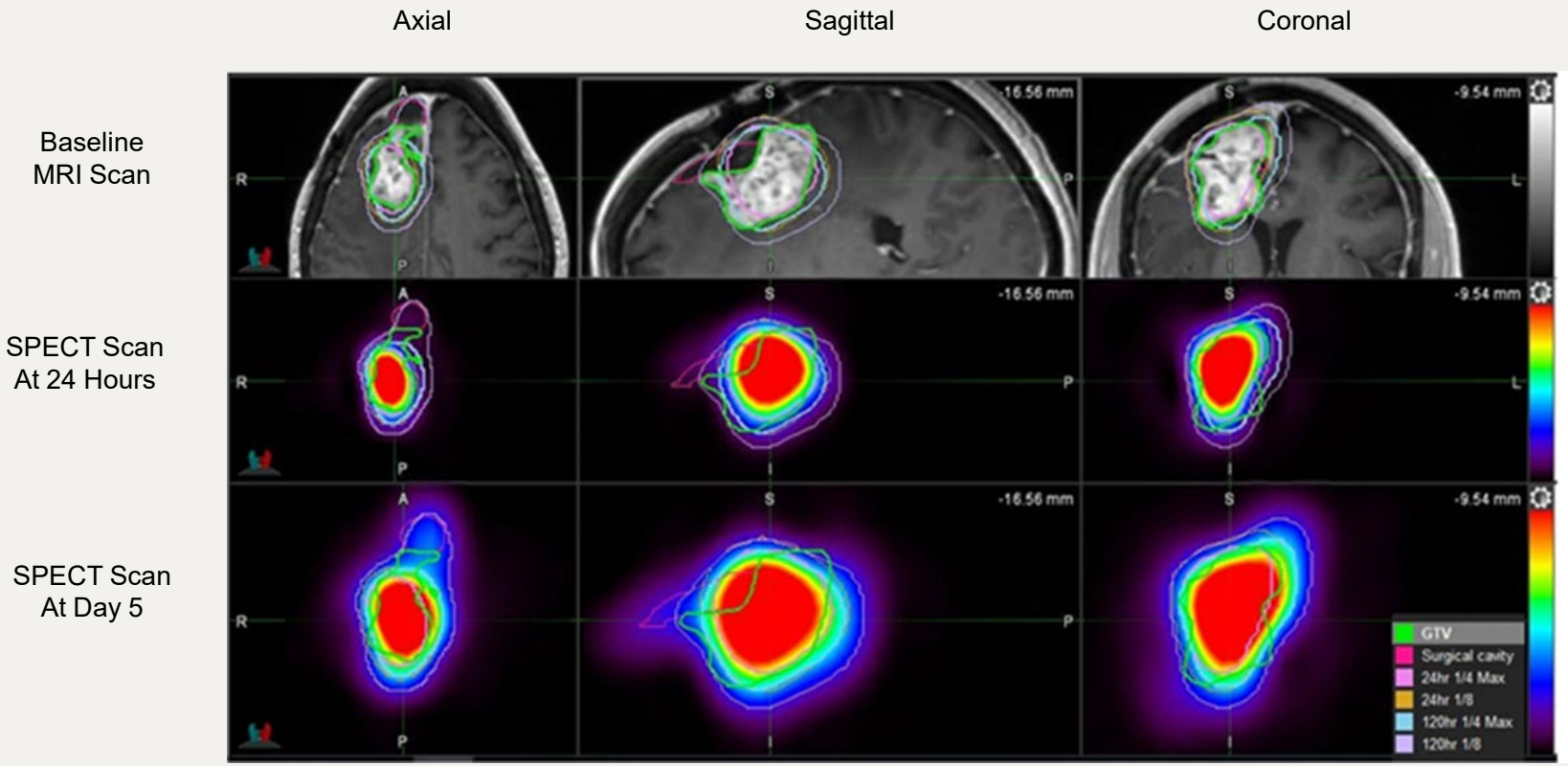
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Subject 01-017



+ Tumor volume was 18.8 mL and tumor coverage was 87%
+ Absorbed dose delivered to tumor was 336 Gy

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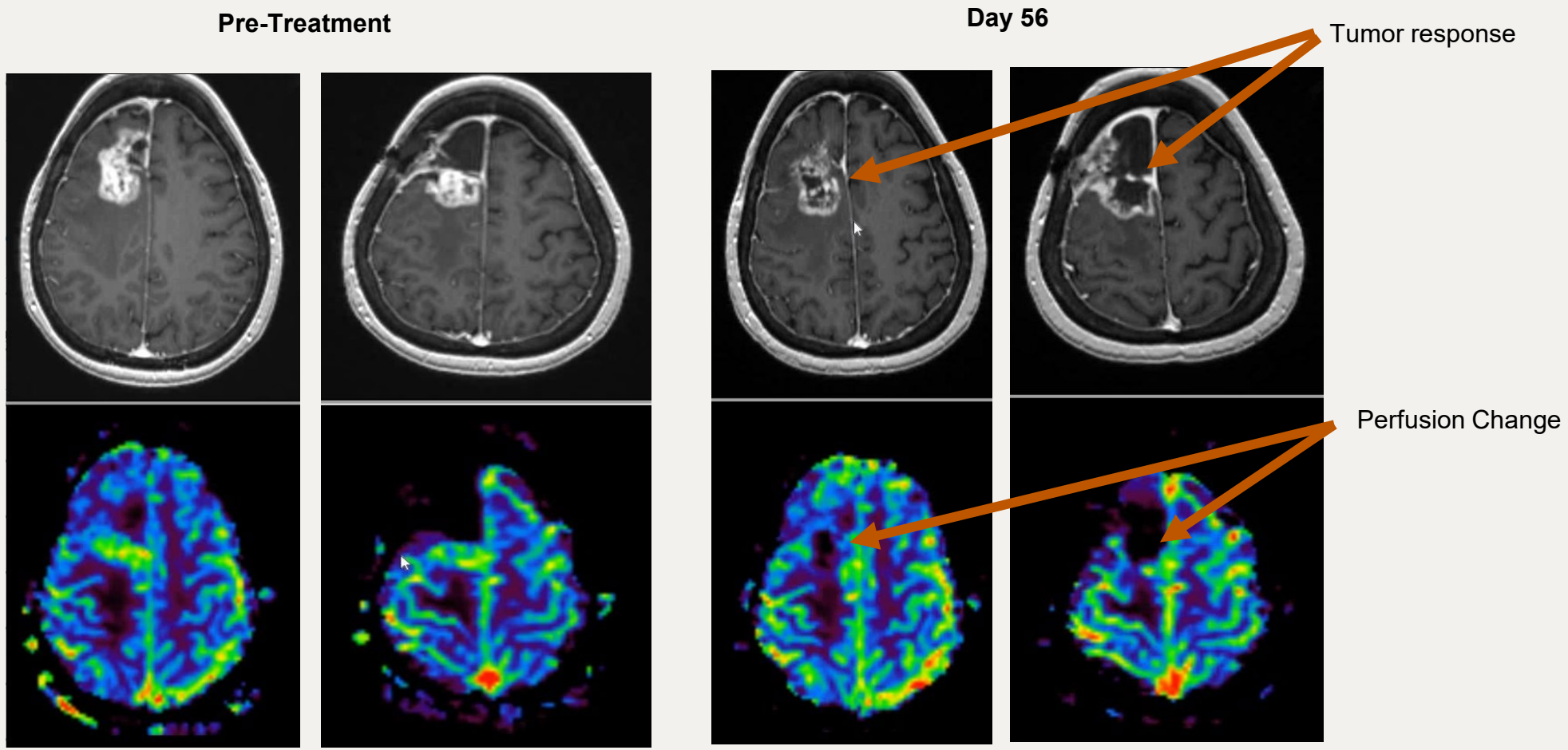
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Subject 01-017



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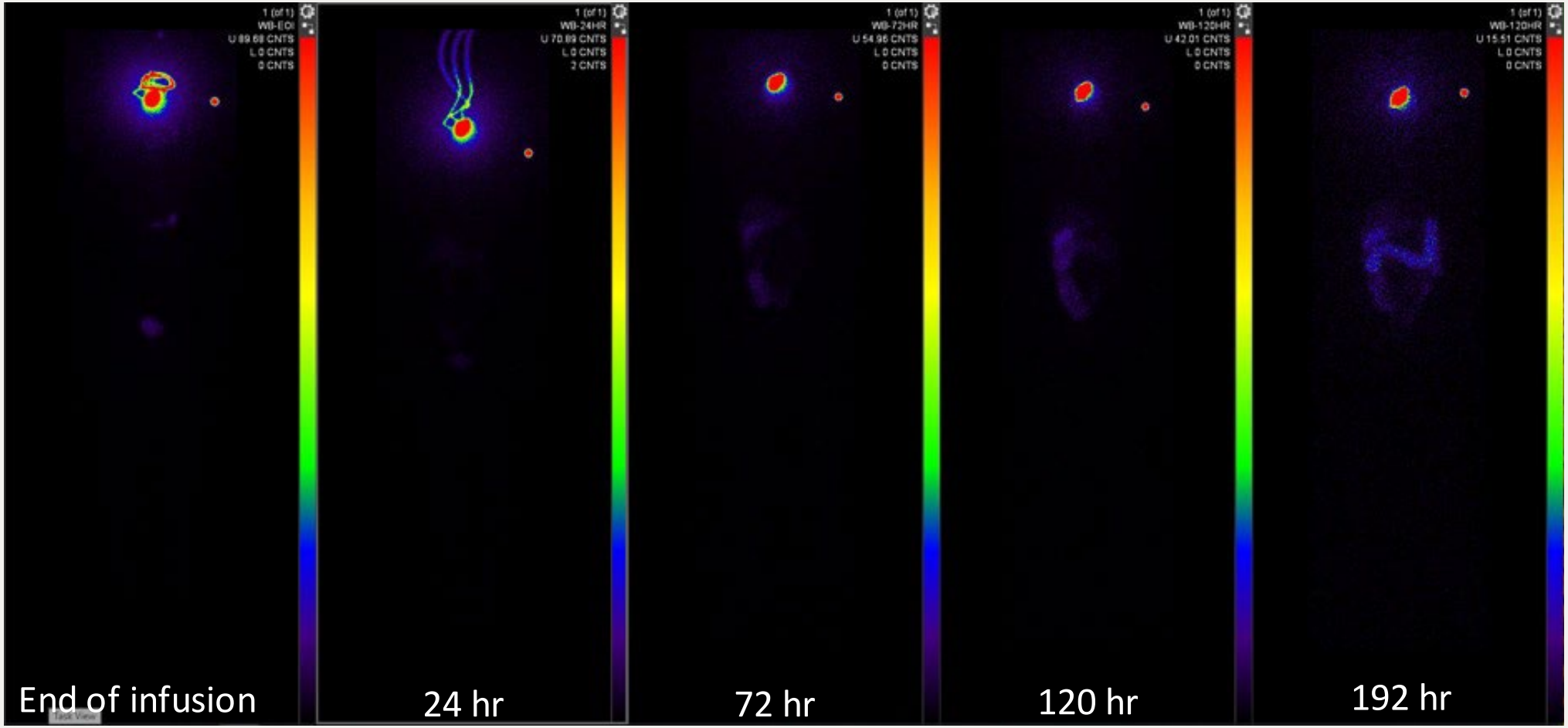
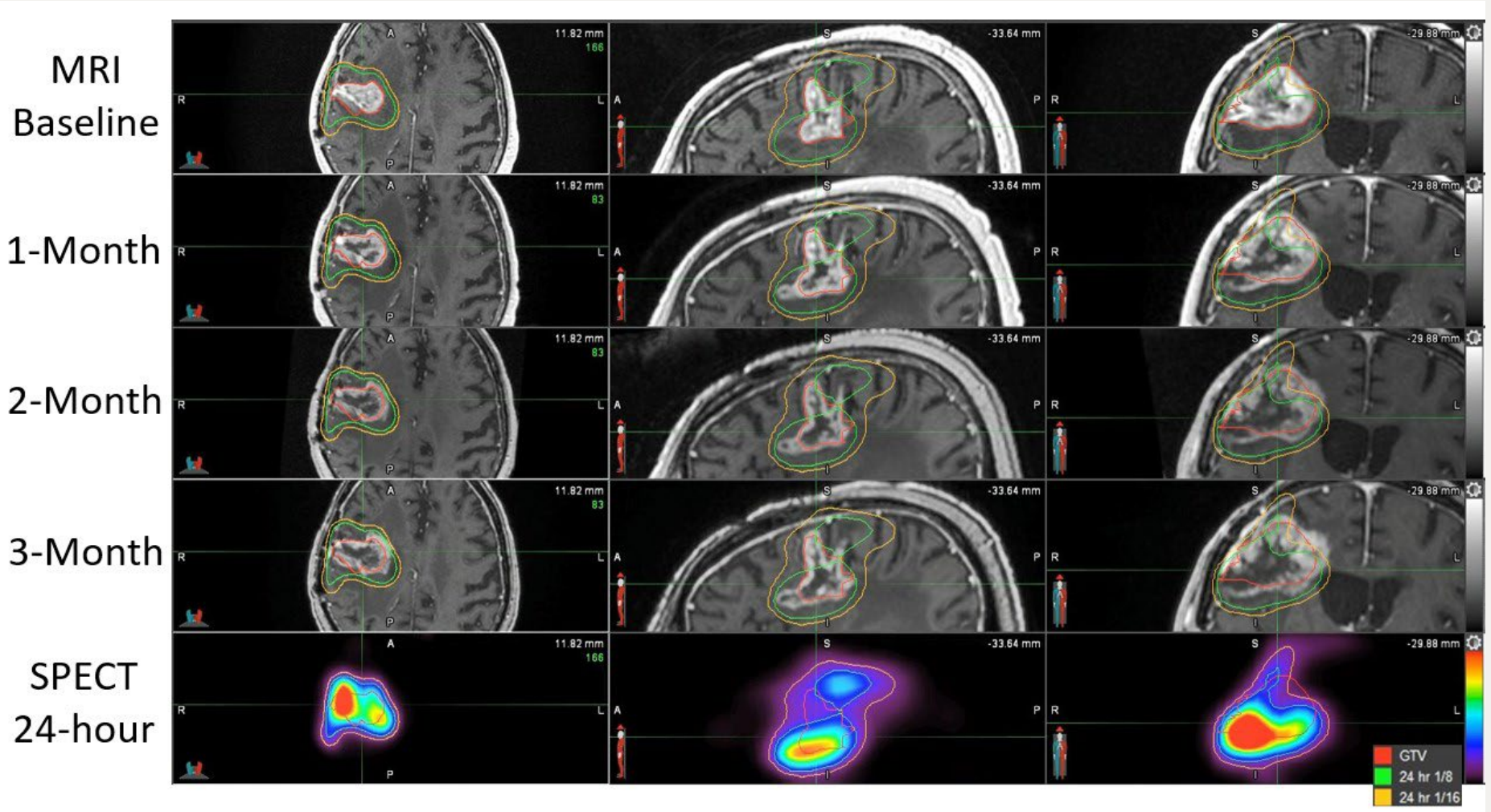
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – No Significant Extracranial Exposure



ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Coverage Correlates with Response



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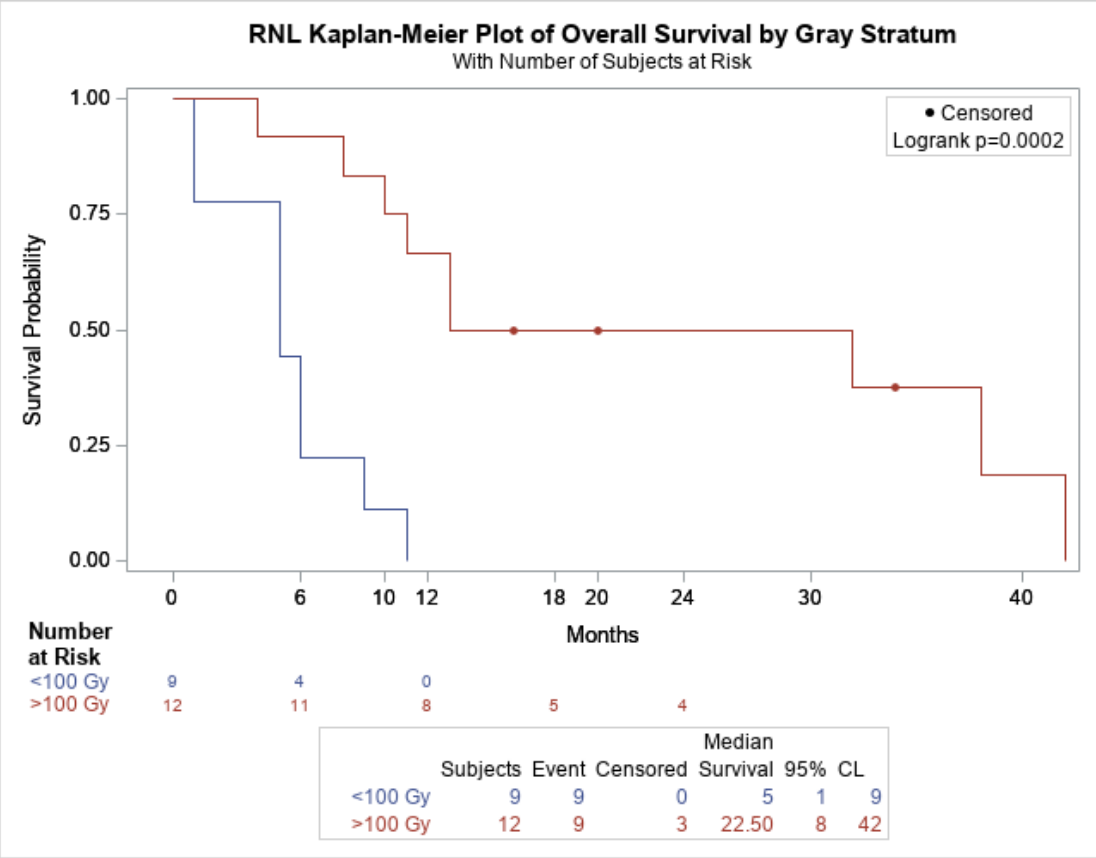
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Data (N=23)



- A statistically significant overall survival benefit in therapeutic doses (>100 Gy) vs. subtherapeutic (p = 0.002)
- In cohorts 5-7 (higher volumes and doses), therapeutic dose achieved in 80% of patients
- Increasing drug volume and radiation correlate with improved overall survival

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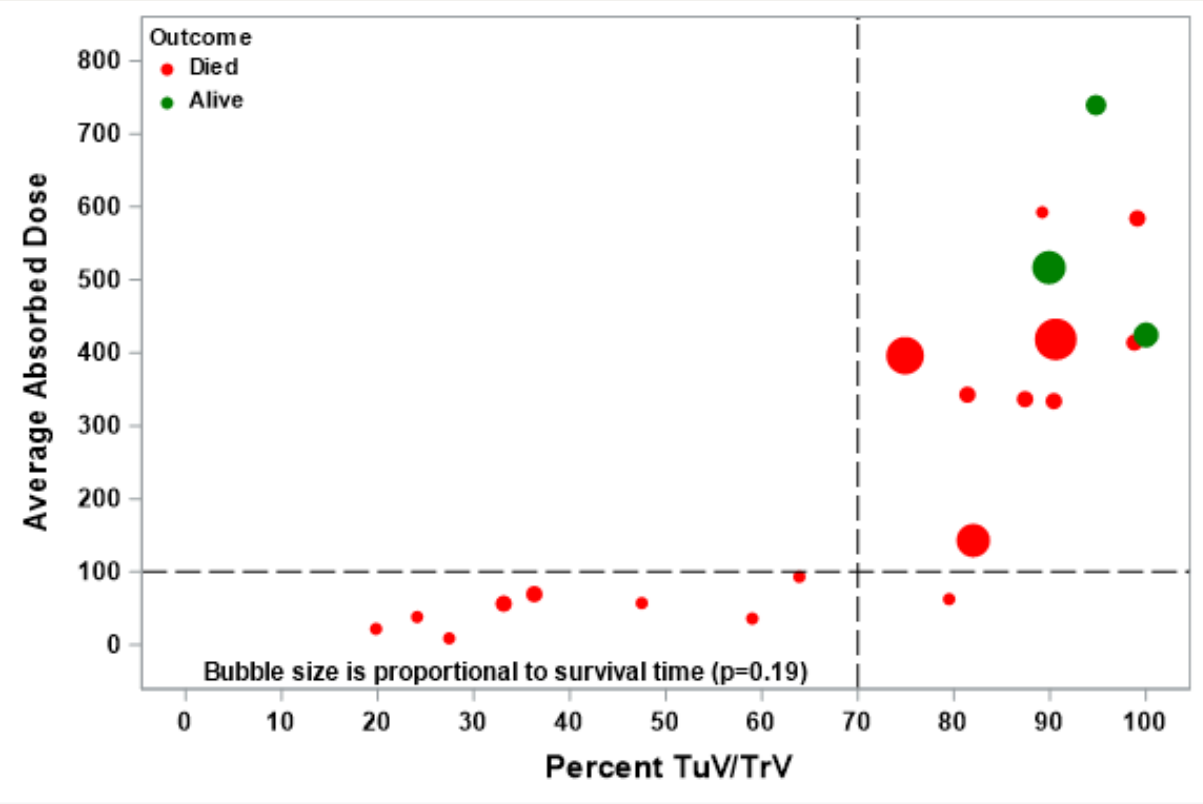
ReSPECT-GBM Phase 1/2a Trial

Phase 1 Dose Escalation – Data (N=23)



Dose (Gy)	Overall Survival (weeks)		
	Median	95% CI	Mean ± SE
<100	**22.3**	6.4, 45.3	24.6 ± 4.8
>100	**129.7**	35, 169.1	100.8 ± 19

- By comparison, **median overall survival of 32.1 weeks** reported in 8 study meta-analysis of 694 recurrent GBM patients treated with bevacizumab monotherapy
- > 100 Gy: 3 patients remain alive, none < 100 Gy

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ReSPECT-GBM Phase 1/2a Trial

Summary

- **Safety**
- Well tolerated, no dose limiting toxicities
- **Delivery and Imaging**
- No dosing failures
- Single administration- up to 20x absorbed dose vs. EBRT (maximum 740 Gy vs. 35 Gy)
- SPECT/CT- reliable real-time visualization and dosimetry
- **Survival**
- A statistically significant OS benefit in therapeutic doses (>100 Gy) vs. subtherapeutic ($p = 0.002$).
- In cohorts 5-7 (higher volumes and doses), therapeutic dose achieved in 80% of patients.
- Increasing drug volume and radiation correlate with improved OS
- **Going Forward**
- Continued Phase 1 dose escalation into Cohort 8
- Phase 2 commencing with 22.3mCi in 8.8mL for GBM ≤20 cm^3 in total volume
- Approved Retreatment protocol commencing
- Peds IND submission (Q4 2022, A Phase 1/2a Trial to Determine the Maximum Tolerated Dose, Safety, and Tolerability of Rhenium-186 Nanoliposome (^{186}RNL) Delivered via Convection Enhanced Delivery (CED) in Supratentorial Recurrent, Refractory, or Progressive Pediatric Ependymoma and High-Grade Glioma (HGG))
- Multi-dose protocol in preparation (Q1 2023)

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THANK YOU

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NIH National Institutes of Health

UT Health San Antonio

UT Southwestern Medical Center

The University of Texas MD Anderson Cancer Center Making Cancer History

+ Our patients and their families

For more information on how to become involved with this trial, please contact:

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